Remarks

Claims 4-10, 12-20, 24-27 are pending.

Claim 3 has been canceled.

Claims 4, 6, 24 and 26 have been amended.

No new matter has been added with the amendments or the addition of the new claims, which are intended to merely clarify language used in the claims and the subject matter claimed. The scope of the claims is intended to be the same after the amendment as it was before the amendment.

Rejection based under 35 U.S.C. § 112(1)

The Examiner maintained the rejection of Claims 3-10, 12-20, 24 and 26 under Section 112(1) for a non-enabling disclosure.

The Examiner maintains that the Claims are not enabled for *any* formulation which comprises an antibody molecule coupled to *any* liposome wherein the formulation binding to HLA-DR protein present at the surface of *any* infectious agent and the membrane of a cell.

The claims have been amended to recite an *anti HLA-DR* antibody molecule coupled to a liposome – and that the liposome comprises *a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol* in a molar ratio of about 10:1 to 1:1 with the acyl chains being either saturated or unsaturated and 14-18 carbon atoms in length.

As such, the term "liposome" in the claims is clearly defined as being limited to the recited mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol, with numerous examples of suitable mixtures being described in the specification. One skilled in the art reading that disclosure would clearly be enabled to practice the claimed invention utilizing liposomes as broadly as claimed without undue experimentation.

As for the term "infectious agent," one of ordinary skill in the art would readily ascertain infectious agents that fall within the scope of the claim other than the HIV virus exemplified in the specification.

The term "infectious agent" is clearly defined in the claims as being limited to those agents having *an HLA-DR protein present at the surface*. Such infectious agents include HIV

virus – as well as the Epstein-Barr virus (EBV), HTLV-1 virus, and Simian Immunodeficiency Virus (SIV). See for example, the enclosed publications as follows:

> Knox et al., "Epstein-Barr Virus Infection of CR2-Transfected Epithelial Cells Reveals the Presence of MHC Class II on the Virion," *Virology* 213:147-157 (1995)
>
> Saifuddin et al, "Transfer of Host T-Cell Membrane HLA-DR and CD25 to Target Cells by Human Retroviruses," *J. Acquired Immune Deficiency Syndromes and Human Retrovirology* 17: 196-202 (1998)
>
> Arthur, L. O. et al., "Cellular Proteins Bound to Immunodeficiency Viruses: Implications for Pathogenesis and Vaccines," *Science* 258: 1935-38 (1992)

The character of the "infectious agent" recited in the claims is well-delineated and a working example is provided that would enable an art worker to obtain and employ other such infectious agents as broadly as they are claimed, particularly based on the knowledge in the art. Clearly, one of ordinary skill in the art would be fully enabled to practice Applicant's invention as broadly as it is claimed utilizing infectious agents other than HIV virus.

Applicant has provided a sufficiently enabling disclosure to meet the requirements of 35 U.S.C. 112, first paragraph. Applicant's disclosure provides reasonable assurance to one skilled in the art that formulations other than the exemplified formulation will possess the indicated utility and provide the stated effect. That is, Applicant's submit that the specification is sufficiently enabling for one of ordinary skill in the art to make and use the invention disclosed and claimed without undue experimentation.

The claims are limited to infectious agents having *an HLA-DR protein present at the surface* and thus do not call for just any infectious agent.

It would be a routine matter for one of ordinary skill reading Applicant's disclosure to determine without undue experimentation whether the formulation was capable of binding to the surface of an infectious agent and to the surface of a cell.

Applicant has provided a sufficiently supporting disclosure, both through the working example and descriptive discussion, to teach those of ordinary skill in the art how to make and use the invention as broadly as it is claimed.

Applicant believes that the present disclosure is fully enabling for liposomes as delineated in the claims and for infectious agents other than the described HIV virus. Accordingly, withdrawal of this rejection is respectfully requested.

Rejection based under 35 U.S.C. § 112(2)

In the Office Action at page 19, the Examiner rejected Claims 24 and 26 under Section 112(2) for the use of indefinite claim language.

Claim 26 has been amended to recite that the formulation is "*capable of*" delivering a drug to the cell and infectious agent.

As suggested by the Examiner, Claims 24 and 26 have been amended to recite "an antigen binding fragment thereof."

It is submitted that the claims as amended are clear in their meaning, and satisfy the requirements of Section 112(2). Accordingly, withdrawal of the rejection under Section 112(2) is respectfully requested.

Rejection of Claims under 35 U.S.C. §§ 102(b) (EP 0286418)

At paragraph 5, the Examiner rejected Claims 10, 12-20 and 24-27 under Section 102(b) as anticipated by EP 0286418 as evidenced by Saarloos. This rejection is respectfully traversed.

The Examiner maintains that EP 0286418 discloses each of the elements recited in the claims and that it would be *inherent* that the formulation would bind to an HLA-DR class II protein on the membrane surface of a cell *and/or* at the surface of an infectious agent.

First of all, the claims recite a formulation that is capable of binding to an HLA-DR protein that is present on *both* the membrane surface of a cell *and* at the surface of an infectious agent.

Secondly, Claims 24 and 26 have been amended to further define the character of the liposome – which the Examiner admits is not disclosed in EP 0286418.

Accordingly, withdrawal of this rejection of the claims is respectfully requested.

Rejection of Claims under 35 USC § 103(a) (EP 0286418)

At paragraph 11, the Examiner rejected Claims 3-9 under Section 103(a) as obvious over EP 0286418 as evidenced by Saarloos, in view of USP 5,773,027. This rejection is respectfully traversed.

The Examiner cites to USP 5,773,027 for teaching a formulation for treating of viral disease such as HIV that comprises a liposome composed of a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol as recited in the claims – including coupling of antibody molecules to the liposome to enhance targeting of the liposome to specific cells, citing to col. 4, lines 11-13.

The Examiner maintains it would be obvious to substitute the liposomes "that coupled to anti-HLA-DR (class II antigen)…as taught by EP 0286418" for the specific liposomes taught by USP 5,773,027.

At page 15, the Examiner referred to his discussion of EP 0286418 as evidenced by Saarloos at page 5, stating as follows (emphasis added):

> …the EP 0286418 A1 *teaches* a formulation which comprises *antibodies or antibody fragments capable of binding to class II antigens* (which is another name for HLA-DR) *present at the surface of an infectious agent such as HIV virus and the membrane of a host cell* such as monocytes or CD4 positive lymphocytes wherein the reference antibody being coupled to a lipid comprising vesicle such as liposome (see page 15, lines 35-38, page 15, lines 20-30, in particular). The reference class II antigens *inherently are HLA-DR protein as evidence by the Saarollos* [sic] *et al* (see page 1640, col. 1, second paragraph, in particular). Because the claimed formulation is the same as that taught by EP028641A1, *the reference formulation inherently binds to* HLA-DR class II protein on T cell such as CD4 lymphocytes and/or HLA-DR class II protein present on HIV virus…..

That a certain result or characteristic *may* occur or be present in the prior art is *not* sufficient to establish the inherency of that result or characteristic. *SmithKline Beecham Corp. v. Apotex Corp.*, 74 USPQ2d 1396 (Fed. Cir. 2005); *Continental Can Company USA v. Monsanto Company*, 20 USPQ2d 1746 (Fed. Cir. 1991); *In re Oelrich*, 212 USPQ 323, 326 (CCPA 1981). In relying upon the theory of inherency, the Examiner must provide factual and technical grounds to support the determination that the allegedly inherent characteristic *necessarily and inevitably* results from the applied prior art. Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.' *In re Robertson*, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)

For the doctrine of inherency to apply it must be *inevitable* that the formulation of EP 0286418 *necessarily* results in the binding to HLA-DR protein on *both* a cell *and* on HIV virus (or other like infectious agent).

The Examiner has provided no such evidence that the EP 0286418 formulation would *necessarily and inevitably* bind to HLA-DR protein on *both* a cell *and* on HIV virus.

In Example 3 (page 15), EP 0286418 merely *speculates* that it would be *useful* to use antibodies to target Class II antigens, stating as follows (emphasis added):

> As mentioned above, *antibodies can be used to target liposomes for interaction with particular cell types* (Weinstein, et al., Biochim. Bophys. Acta 509:272-288 (1978). In the context of AIDS, *it will be useful to target the CD4 and Class II antigens* (as parts of the HIV binding site), …and other antigenic determinants characteristic of either the virus or the host cell….

First, contrary to the Examiner's assertion, EP 0286418 does *not* describe liposomes bearing anti-Class II antigens.

Rather, Example 3 of EP 0286418 teaches liposomes bearing antibodies to target *Fc receptors* – antigen H-$2K^k$ – in monocytes and macrophages that function in the uptake of opsonized particles. See at page 15, lines 38-47 (emphasis added):

> …It will also be useful to target Fc receptors and other receptors responsible in monocytes and macrophages for uptake of opsonized particles. This may enhance the effectiveness of liposomes containing chain terminators in inhibiting viral growth in these cells. *Hence, Fc receptors were targeted by attaching mouse IgG (including the Fc portion) to liposomes.* Of course, it would also be possible to attach only the Fc domain or a portion thereof to serve the same purpose.
>
> To produce antibody-bearing liposomes, a modification of the method described by Leserman, et al. (Nature 288:602-604 (1980)) was used. The antibody selected for the study was 36-7-5, *a murine IgG2a reactive with H-$2K^k$*. The object was to "opsonize" liposomes *for uptake by Fc receptors on the monocyte lineage and other cell types.*

Second, EP 0286418 does not teach coupling antibodies composed of diacylphosphatidylcholine and diacylphosphatidylglycerol as claimed.

Rather, Example 3 teaches coupling antibodies to liposomes composed of phosphatidylcholine (EPC), phosphatidylserine (PS), cholesterol, N-[4-(p-maleimidophenyl)butyryl] phosphatidylethanolamine (MPB-PE), ^{14}C-cholesteryl oleate, and 2',3'-dideoxycytidine-5'-triphosphate (ddCTP).

EP 0286418 does *not* describe liposomes bearing anti-Class II antibodies, and particularly not anti-Class II antibodies bound to liposomes composed of diacylphosphatidylcholine and diacylphosphatidylglycerol.

Thus, even if, *arguendo*, one were to bind an anti-HLA-DR antibody to a liposome – *based on the teaching of EP 0286418*, the liposomes would be those utilized in Example 3 – composed of phosphatidylcholine, phosphatidylserine, cholesterol, and MPB-PE.

Furthermore, although Saarloos discloses that HLA-DR (Class II MHC) was associated with *in vivo* sources of HIV-1 virions from primary isolates, macrophages and blood plasma using an immunocapture method with an anti-HLA-DR antibody, the results showed that the anti-HLA-DR antibody captured only about 50% of HIV_{Ada-M} and HIV_{Ba-L} *monocytotropic virus*, and four of eight samples of *plasma virus did not detectably bind* to the anti-HLA-DR antibody (Saarloos at page 1641, 2nd col., 2nd ¶).

Saarloos further states that it was *unexpected* that HLA-DR was *not detected* on all plasma virus samples tested – and further indicated that *HLA-DR levels on monocytes can substantially decrease* during HIV infection, stating as follows (at page 1642, 1st col., 1st ¶):

> …It was somewhat unexpected, then, to find that HLA-DR was not detected on all of the plasma virus samples tested.…Alternatively, it is possible that plasma virus from samples testing negative for HLA-DR was derived from cells that expressed lower levels of HLA-DR in vivo. *In fact, Clerici et al. have observed that HLA-DR levels on monocytes can substantially decrease during HIV infection (7)…Thus, the variation in levels of HLA-DR expression on plasma virus may be due to the plasma virus budding from more than one cell type or, alternatively, from several subpopulations of one cell type.*

One skilled in the art reading Saarloos' disclosure would not expect that an anti-HLA-DR antibody would *necessarily and inevitably* bind to HLA-DR protein on *both* a cell *and* on HIV virus – *much less an antibody coupled to a liposome*.

At most, Saarloos' disclosure presents an "obvious-to-try" situation -- that is, a general disclosure that suggests further investigation, but does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. *In re Eli Lilly & Co.*, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990).

With respect to obvious to try, two types of errors are generally recognized. *In re Fine*, 5 U.S.P.Q.2d 1596, 1599 (Fed. Cir. 1988); *In re O'Farrell*, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988).

The error committed by the Examiner is the case in which what "is obvious to try" is to explore a new technology or general approach that seems to be a promising field of experimentation where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

The mere disclosure in Saarloos of the presence of HLA-DR associated with HIV-1 virions does not provide an art worker with adequate guidance for preparing a *liposome-bound* anti-HLA-DR antibody with the expectation that will be reactive with *both* HIV-1 virus *and cells.*

Given the unpredictability of the binding of an anti-HLA-DR antibody with HIV-1 virions and the level of HLA-DR expression in monocytes according to Saarloos, there would be no reasonable expectation of success that a *liposome-bound* anti-HLA-DR antibody will be reactive with *both* HIV-1 virus *and cells.*

The cited references do not provide the proper motivation to modify the EP 0286418 composition from the antibody-bound liposomes taught by EP 0286418 in Example 3 to Applicant's liposome formulation as claimed – *nor an expectation of success* of Applicant's formulation to successfully bind both HIV-1 virus *and* cells.

Therefore, it is submitted that nothing in the cited references, either alone or in combination, disclose or suggest the presently claimed formulations, and withdrawal of this rejection is respectfully requested.

Rejection of Claims under 35 USC § 103(a) (Selvam or Desormeaux)

At paragraph 8, the Examiner rejected Claims 10, 12-18 and 24-27 under Section 103(a) as obvious over Selvam (*Antiviral Research* 33: 11-20, 1996) or Desormeaux (*J. Drug Targeting* 6(1):1-15, 1998) in view of Saarloos and Cantin (*J. Virology* 71(3):1922-1930, March 1997)

At paragraph 9, the Examiner rejected Claims 3-9 and 19 under Section 103(a) as obvious over Selvam or Desormeaux in view of Saarloos and Cantin, and further in view of USP 5,773,027 (June 30, 1998).

At paragraph 10, the Examiner rejected Claim 20 under Section 103(a) as obvious over Selvam or Desormeaux in view of Saarloos and Cantin, and further in view of Harlow (*in Antibodies: a Laboratory Manual*, 1988, Cold Spring Harbor publication, pages 626-629).

These rejections are respectfully traversed.

The Examiner maintains that it would be obvious to substitute the anti-CD4 antibody or combine the anti-CD4 antibody coupled to a liposome as taught by Selvam or Desormeaux with an anti-HLA-DR ligand based on Saarloos. The Examiner relies on Saarloos for teaching an anti-HLA-DR ligand that "*binds to the surface of HIV and at the membrane surface of T cells.*"

The Examiner further stated (page 7, emphasis added):

> ...From the combined teachings of the references, it is apparent that one of ordinary skill in the art *would have had a reasonable expectation of success* in producing the claimed invention."
> ...Saarloos...teach a ligand such as anti-HLA-DR (class II MHC) that binds to HLA protein present at the surface of an infectious agent such as HIV *and at the membrane surface of a cell such as CD4+ T cells and macrophage* (see entire document, page 1641, col. 2, ***page 1642, col. 1, in particular***)...

The Examiner's statement regarding Saarloos is in error.

Saarloos does not teach an anti-HLA-DR ligand that binds to HLA protein present at the surface of HIV *and* at the membrane surface of a cell. At page 1642, col. 1, cited by the Examiner, Saarloos discloses that

1) HLA-DR was shown to be associated with plasma virus;
2) HLA-DR was *not* detected on all plasma virus samples;
3) Plasma virus samples that tested negative for HLA-DR may have been "derived from cells that expressed lower levels of HLA-DR in vivo"; and
4) HLA-DR levels on monocytes can *substantially decrease during HIV infection.*

Contrary to the Examiner's assertion, Saarloos does *not* disclose binding an anti-HLA-DR ligand to HLA protein present at the membrane surface of a cell.

Saarloos merely demonstrated that HLA-DR antibody immunoprecipitated HIV virions. And Saarloos' results showed that the anti-HLA-DR antibody captured only about 50% of monocytotropic virus – and four of eight samples of *plasma virus did not detectably bind* to the anti-HLA-DR antibody (Saarloos at page 1641, 2nd col., 2nd ¶). In addition, Saarloos indicated that *HLA-DR levels on monocytes can substantially decrease* during HIV infection. See page 1642, 1st col., 1st ¶ (cited above).

Given the unpredictability of the binding of an anti-HLA-DR antibody with HIV-1 virions and the level of HLA-DR expression in monocytes according to Saarloos, one skilled in the art reading Saarloos' disclosure would not expect that an anti-HLA-DR antibody would

necessarily and inevitably bind to HLA-DR protein on *both* a cell *and* on HIV virus – *much less an antibody coupled to a liposome.*

As discussed above, at most, Saarloos' disclosure merely presents an "obvious-to-try" situation by suggesting further investigation, but does not contain a sufficient teaching that the claimed result would be obtained if certain directions were pursued. *In re Eli Lilly & Co.*, 14 USPQ2d 1741, 1743 (Fed.Cir. 1990).

Therefore, it is submitted that nothing in the cited references, either alone or in combination, disclose or suggest the presently claimed formulations, and withdrawal of this rejection is respectfully requested.

Extension of Term. The proceedings herein are for a patent application and the provisions of 37 CFR § 1.136 apply. Applicant believes that a three-month extension of term is required. Please charge the required fee (large entity) to Account No. 23-2053. If an additional extension is required, please consider this a petition therefor, and charge the required fee to Account No. 23-2053.

Based on the above remarks, the Examiner is respectfully requested to reconsider and withdraw the rejections of the claims. It is submitted that the present claims are in condition for allowance, and notification to that effect is respectfully requested.

Respectfully submitted,

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